REMARKS/ARGUMENTS

Claims 50, 69-70 and 73-89 have been cancelled, but may be pursued in a future related application. Claim 90 has been amended to specify that the amyloid deposit is of Aβ as described in the specification at e.g., p. 12, lines 27-28. Claim 90 has also been amended to specify a reduction in the level of amyloid deposit is monitored as described in the specification at e.g., p. 35, lines 10-15. Claim 99 has been cancelled as redundant. Minor amendments have been made to correct claim dependency 94, and in various claims to refer to "amyloid deposit" in the singular form for consistency. As per normal construction of patent claims, reference to the singular form is intended to include the plural. After entry of this amendment, claims 90-98 and 100 are pending. Claim amendments and cancellations should not be construed as acquiescence in any ground of rejection. Applicants respond to the Examiner's comments using the paragraph numbering of the office action.

7. For purposes of responding to the present office action, applicants accept the Examiner's determination of priority to May 26, 2000. The Cross-Reference to Related Applications was amended to delete reference to 09/322,289 in an amendment of February 9, 2004. Applicants reserve the right to provide evidence of earlier invention, should it become relevant in this or any subsequent proceedings.

8. The objections to claims 50, 81, and 87 are moot in view of cancellation. Claim 90 has been amended as suggested.

9-10. Rejections under 35 USC 112, second.

The rejection of claim 74 is moot in view of cancellation of this claim.

11. The rejection of claim 75 is moot in view of cancellation of this claim. Dependency of claim 94 has been corrected.

12-13. Claims 50, 69-70, 77-79, 81-84 and 87-89 stand rejected as allegedly anticipated by Belloti as further evidenced by Benjamini. This rejection is moot in view of claim cancellations.

14. Claims 81-83 and 85-86 are rejected as allegedly anticipated by Jahrling as further evidenced by Benjamini. This rejection is moot in view of claim cancellations.

15. Claims 50, 69-70, 78, 81-83, 85 and 87-88 are rejected as allegedly anticipated by Jorbeck. This rejection is moot in view of claim cancellations.

16. Claims 50, 69-70, 77, 79, 81-82, 84, 87 and 89 are rejected as allegedly anticipated by Herlyn as further evidenced by Benjamini. This rejection is moot in view of claim cancellations.

17. Claims 60, 69, 70, 73, 77-79, 81-84, 87-92, 96-97 and 99 are rejected as allegedly anticipated by Solomon, WO 99/60024. Solomon is alleged to teach in vivo and in vitro methods of amyloid removal with anti-amyloid antibodies that enhance the cell-mediated response to deposits of amyloid. In particular, the Examiner alleges that Figures 2A and 2B show in vitro adherence of human neutrophils after amyloid plaques were treated with anti-human immunoglobulin light chain (IgLC) monoclonal antibodies. Insofar as the rejection was directed to claims 60, 69, 70, 73, 77-79, 81-84, and 87-89, it is moot in view of the cancellation of these claims. Insofar as the rejection was directed to claim 90, it is now moot in view of the amendment to specify an amyloid deposit of Aβ. The amyloid used by Solomon was of the human immunoglobulin light chain (see p. 17, lines 24). Applicants also note disagreement with the Examiner's position that Solomon teaches an opsonizing (i.e., clearing) effect of antibodies to amyloid material in vitro. Figs. 2A and 2B of Solomon show merely binding of neutrophils to deposits of IgLC treated with antibodies, not clearing.

18. Claims 50, 69-79, 73, 74-84 and 87-100 stand rejected as allegedly anticipated by Vitek as further evidenced by Benjamini. Vitek is alleged to teach that an AGE-bearing targeting agent can be tested for efficacy in vitro or in vivo (citing to the paragraph spanning columns 21 and 22, column 22, line 54 to column 23, line 4 and column 24, lines 13-25). The Examiner cites column 32, Example 2 as allegedly disclosing that in vitro analysis may be performed in tissue sections viewed and fixed in vitro. The Examiner cites Benjamini as allegedly teaching that ADCC assays are widely accepted in the art, and include cytolysis mediated via antigen/antibody binding. The Examiner relies on Vitek's discussion of polyclonal antibodies for an antibody binding to an epitope within Aβ1-7. This rejection is respectfully traversed.

The Examiner's comments regarding Vitek in the present office action are substantially similar to those in previous office actions; however, the Examiner has not commented on the distinctions pointed out by applicants. Specifically, applicants pointed out that Vitek's method differs from that claimed in at least two respects: (1) Vitek does not disclose simultaneous presence of an antibody and phagocytic cells in an *in vitro* clearing reaction: and, (2) nor does it disclose that the clearing reaction screens an antibody for clearing activity. Although Vitek discusses various methods of treatment and diagnosis, only a small portion of the patent relates to an *in vitro* assay for phagocytosis at col. 22, lines 54-66. As discussed in the last response and reiterated below, the assay discussed at col. 22, lines 54-66 is not the same as that claimed. In Vitek's *in vitro* assay, the object is not to screen an antibody but rather to screen AGE -TF (thioflavin) for capacity to modify insoluble or aggregated Aβ (col. 22, lines 53-55). This is achieved by the following steps. First, AGE-TF is contacted with aggregated Aβ. The incorporation of AGE-TF into aggregated Aβ is then tested by ELISA using an antibody (col. 22, lines 58-61). The antibody in this step is used simply as a conventional diagnostic reagent, and is not itself being screened for anything. After verifying incorporation of AGE-TF, phagocytic cells are added to test for clearance of AGE-TF modified Aβ (col. 22, lines 61-65). However, at the time the phagocytic cells are added, there is no indication that the antibody used for the ELISA is still present. It would be most logical and typical practice when performing a diagnostic step on an intermediate product in a process to perform the diagnostic step on only a sample of the intermediate so as to avoid influencing the further processing of the intermediate by contamination with the reagents in the diagnostic step. In any event, insofar as there is doubt as to whether Vitek proposes adding phagocytic cells to the same or a different vessel to that in which the ELISA using antibody to AGE-TF is performed, that doubt should inure to the benefit of applicants given that the burden of proof rests on the PTO (*In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)).

As noted, the present office action does not comment on the above remarks but instead cites to some additional sections of Vitek and to Benjamini as a secondary reference. These additional citations will be addressed in turn. The paragraph spanning cols. 21-22 of Vitek merely reiterates what applicants have stated above, namely, that Vitek is screening an

AGE bearing targeting agent ("The effectiveness of an AGE bearing targeting agent, such as AGE-TF or AGE-Congo Red, can be tested in vitro, and in vivo for efficacy at AGE modification of amyloid"). An AGE bearing targeting agent is a compound such as AGE-TF or AGE-Congo Red, not an antibody.

The paragraph spanning cols. 22 and 23 of Vitek discusses a binding assay not a clearing assay (see col. 22, line 67). Moreover, the paragraph refers to "[i]nvolvement of *AGE-receptor-mediated* uptake by phagocytic cells" (col. 22, line 66-67, emphasis supplied) suggesting that phagocytic cells bind to AGE-receptors, rather than antibody FC domains.

Column 24, lines 13-25 of Vitek refers to "detecting the amount of amyloid in affected tissues, and comparing that amount to the amount in control animals..." The references to "affected tissues" and "control animals" suggest an in vivo assay, not an assay in which an amyloid deposit is combined with an antibody and phagocytic cells in vitro, as claimed.

Col. 32, example 2 of Vitek reports staining of tissue sections from an infected hamster brain with antisera to prion protein and to AGE to show co-localization of the two sera. The assay used antibodies for detection, and not to screen them for clearing activity in the presence of phagocytic cells. Thus, none of the sections of Vitek cited by the Examiner discloses or suggests a method of screening an antibody as claimed.

Although not expressly stated, the Examiner's reliance on Benjamini appears to be based on a theory of inherency. However, "[i]nherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis supplied). Here, as discussed at length above and in previous responses, Vitek discusses a clearing assay involving AGE-modified Aβ and phagocytic cells but does not say that an antibody is present. Benjamini indicates that one possible mechanism of phagocytic cells is to bind to receptors present on antibodies, but does not say that this is the only mechanism. Paul, Immunology (3rd Ed., Raven Press,1993) at p. 942, second column, second paragraph indicates that as of 1993 phagocytic cells were known to recognize at least forty other kinds of receptor. As noted above, Vitek refers to "[i]nvolvement of *AGE-receptor-mediated*

uptake by phagocytic cells" (col. 22, line 66-67, emphasis supplied) suggesting a mechanism in which phagocytic cells bind to AGE-receptors not antibodies. Given the number of receptors on phagocytic cells and Vitek's comments regarding phagocytic cell uptake being mediated by AGE-receptors, it cannot be concluded that antibodies must necessarily be present in Vitek's assay. Thus, the requirements for inherent anticipation have not been met. For this reason, as well as the others discussed above, and in previous responses, it is respectfully submitted the rejection should be withdrawn.

19. Claims 50, 69-70 and 73-100 stand rejected as obvious over Vitek as further evidenced by Benjamini, Solomon, Herlyn, Jarling, Bellotti and Jorbeck. Vitek is cited as above. The Examiner acknowledges that Vitek does not teach methods in which an antibody binding within Aβ1-7 is administered to a sample from Alzheimer's patient. Benjamini, Solomon, Herlyn, Jarling, Bellotti and Jorbeck are cited as allegedly teaching that one of skill in the art is highly versed in assessing the ability of any antibody to mediate clearance of an antigen or cell via phagocytosis or cytolysis. The Examiner alleges that one would have been motivated to assess such activity in vitro given the successful teachings of the AGE-beta amyloid antibody in vivo as taught by Vitek. This rejection is moot as applied to claims 50, 69, 70, 73-89, and 99, which have been cancelled. This rejection is respectfully traversed insofar as applied to the pending claims.

As a preliminary matter, applicants note the rejection is unclear as to what teachings from the respective references are being combined and against which claims. The only deficiencies in Vitek acknowledged by the Examiner are lack of teaching of an amyloid sample from an Alzheimer's patient, and lack of teaching of an antibody binding to within Aβ1-7. These are features of claims 93, 98 and 100. However, the Examiner does not indicate that the rejection is confined to these claims, nor does she indicate where the teaching of an amyloid sample from an Alzheimer's patient or an antibody binding within Aβ1-7 is found in any of the secondary references. With respect to other claims subject to the rejection, the Examiner does not acknowledge any deficiency in the teaching of Vitek; thus, it is unclear with what element of each of the secondary references Vitek is proposed to be combined and in what manner. "Broad

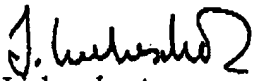
conclusory statements regarding the teaching of multiple references" are insufficient to establish obviousness, *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Insofar as the rejection can be understood, applicants offer the following comments. As was noted above, all of the pending claims differ from Vitek in requiring a step of combining an amyloid deposit of Aβ, an antibody to be screened and phagoyctic cells in vitro. Vitek only discusses combining AGE-modified Aβ and phagocytic cells in vitro, and proposes a theory whereby the phagocytic cells bind to AGE receptors. Vitek's discussion of an antibody to AGE-Aβ in vivo would not have suggested modification of the in vitro assay because, among other reasons, Vitek did not show success of the antibody in vivo, or that it operated by a phagocytic mechanism in vivo. Nothing in the secondary references suggests modification of Vitek's assay because none of the cited references concerns in vitro assays for phagocytosis of amyloid deposits of Aβ. For example, Belloti discusses assays on B-cells, Jarling discuses assays on alphaviruses, Herlyn discusses assays on various cancer cells, Solomon discusses a binding assay on deposits of human IgLC, Jorbeck discusses assays on PEC exudates, and Benjamini is a textbook generally discussing mechanism of antibodies and phagocytic cells. None of the secondary references suggest that antibodies could or should be screened for activity in clearing an amyloid deposit of Aβ in vitro.

Insofar as the rejection is directed against claims 93, 98 and 100, the claims are further distinguished from Vitek in that Vitek does not disclose performing an in vitro assay on an amyloid deposit from an Alzheimer's patient or an animal model with Alzheimer's pathology, nor a monoclonal antibody binding within residues 1-7 of Aβ. The Examiner appears to acknowledge these deficiencies, but has not identified any compensatory teaching in the secondary references. Accordingly, claims 93, 98 and 100 are distinguished on additional grounds.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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